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Title: Recent efforts to dissect the genetic basis of alcohol use and abuse

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Abstract (202 words)

Alcohol use disorders (**AUD**) are defined by several symptom criteria, which can be further dissected at the genetic level. Over the past several years, our understanding of the genetic factors influencing alcohol use and abuse has progressed tremendously; hundreds of loci have now been implicated in different aspects of alcohol use. Previously known associations with alcohol metabolizing enzymes (*ADH1B*, *ALDH2*) have been definitively replicated. Additionally, novel associations with loci containing the genes *KLB*, *GCKR*, *CRHR1* and *CADM2* have been reported. Downstream analyses have leveraged these genetic findings to reveal important relationships between alcohol use behaviors and both physical and mental health. AUD and aspects of alcohol misuse have been shown to overlap strongly with psychiatric disorders, whereas aspects of alcohol consumption have shown stronger links to metabolism. These results demonstrate that the genetic architecture of alcohol consumption only partially overlaps with the genetics of clinically defined AUD. We discuss the limitations of using quantitative measures of alcohol use as proxy measures for AUD, and outline how future studies will require careful phenotype harmonization to properly capture the genetic liability to AUD.

Introduction

Alcohol abuse is a global problem, constituting the seventh leading risk factor for death and disability (1). Worldwide, over 100 million people had an alcohol use disorder (**AUD**) in 2016. Statistics from the National Survey on Drug Use and Health show that >85% of adults in the United States report ever having consumed alcohol, with >25% reporting binge drinking in the past month (2). The proportion of adults in the United States with an AUD is estimated to be 6.2% (2). Alcohol use behaviors are complex, and how and why people drink is partially influenced by genetic factors. However, identifying the genetic factors that increase the risk for harmful drinking has been challenging, partially because patterns of alcohol use are dynamic across the lifespan. The terms used to describe alcohol use and abuse are as diverse as the behaviors themselves. *Hazardous drinking* describes heavy drinking that places an individual at risk for future harm. *Harmful drinking* and alcohol *abuse* are defined as drinking that causes mental or physical damage to the individual. These descriptive terms were devised to identify individuals who would benefit from brief interventions and are assessed using screening questionnaires such as the Alcohol Use Disorders Identification Test (**AUDIT**). Alcohol dependence (**AD**) was, until recently, defined according to the DSM-IV and required the presence of 3 or more of 7 criteria in a 12-month period. The DSM-IV made a distinction between alcohol abuse and dependence that was removed under DSM-V and replaced with 'mild' to 'severe' definitions of AUD. Genetic studies encompass the wide range of alcohol use phenotypes; in this review we mirror the language used in the original studies.

AUD can be viewed as the end point of a series of transitions (**Figure 1**), which begin with the initiation of use, continue with the escalation to hazardous drinking and culminate in compulsive harmful use that persists despite negative consequences. Genome-wide association studies (**GWAS**) have been instrumental in discovering novel genetic loci associated with multiple psychiatric conditions. In the field of AUD genetics, studies have mostly focused on either levels of consumption or AUD diagnosis. Recent GWAS have now begun to identify hundreds of genome-wide significant variants, and provide evidence that the components of alcohol use behavior have a distinct genetic architecture.

In this review, we provide an overview of recent molecular genetic findings of alcohol use behaviors from the largest GWAS performed to date. Other reviews have elegantly summarized findings from twin and family studies of heritability, linkage, candidate gene and GWAS [e.g. (3–6)], and we extend on recent reviews of the molecular genetics of AUD (7–9) by including additional GWAS of alcohol use behaviors that identify genome-wide significant hits ($P\text{-value} < 5 \times 10^{-8}$). In addition, we discuss the application of polygenic methods, which provide mounting evidence that alcohol use and misuse are partially distinct. Finally, we delineate future directions to investigate the different etiologic sources that underlie the life course of alcohol use behaviors.

Design strategies for enhancing AUD genetic discovery

For decades, candidate gene studies were used to determine the contribution of specific genes that increase risk for AUD. Candidate gene studies tended to focus on genes that influenced pharmacokinetic and pharmacodynamic (e.g. dopaminergic, glutamatergic and opioid signaling systems) factors. Larger genetic studies have generally not replicated the findings from candidate gene studies (10). One exception to this are the genes encoding ethanol metabolizing enzymes, particularly alcohol dehydrogenase (*ADH*) and aldehyde dehydrogenase (*ALDH*), which have repeatedly been shown to have the largest impact on alcohol consumption and risk for AUD (7).

As study designs have evolved to incorporate GWAS, researchers have been able to scan the whole genome without any hypotheses about the underlying biology of alcohol use behaviors. Initial efforts focused on collecting clinically-defined cases of AUD, but these ascertainment strategies could not amass the large sample sizes required for GWAS (11). Accordingly, multi-ethnic and clinically-defined samples have been combined through the Psychiatric Genomic Consortium of Substance Use Disorders (**PGC-SUD**) working group. The efforts of the PGC-SUD have led to a trans-ancestral meta-analysis consisting of almost 15,000 AD cases and almost 38,000 controls from 28 independent cohorts (12), identifying a single locus (*ADH1B*), which was robustly associated with AD. More recently, using information from electronic health records to infer AUD status, a GWAS of 274,424 multi-ethnic individuals from the Million Veterans Program (**MVP**) cohort identified

10 loci associated with AUD (including *ADH1B*) (18). Kranzler et al (18) showed that alcohol consumption and AUD were genetically correlated but distinct, thus allowing them to adjust for consumption in the AUD GWAS and for AUD in the GWAS of consumption.

In parallel with these efforts, which have focused on clinical diagnoses, other GWAS have incorporated continuous measures of alcohol use. These include self-reported weekly alcohol intake or the scores from screening questionnaires such as the AUDIT (13). The AUDIT can be decomposed to provide a measure of alcohol use from the first 3 questions (**AUDIT-C**) and misuse from questions 4-10 (**AUDIT-P**). These quantitative measures are available in large population-based cohorts such as the UK Biobank (**UKB**), MVP and 23andMe. The GWAS meta-analysis of AUDIT identified 10 associated risk loci (14). Large consortia were also formed to collate quantitative measures of alcohol use, including AlcGen (15) and the GWAS & Sequencing Consortium of Alcohol and Nicotine Use (**GSCAN**). GSCAN have recently identified nearly 100 loci associated with alcohol consumption (17). The MVP study (18) also examined alcohol consumption, allowing for an explicit comparison between AUD and consumption in a single population; of the 18 loci detected in that study, 5 were common to both AUD diagnosis and alcohol consumption.

As the prior two paragraphs make clear, population based cohorts have provided larger sample sizes, which are critical for obtaining adequate power for GWAS. Their use can come at the cost of missing more severe alcohol use phenotypes. For example, the frequency of AUD in the UKB is lower than the population average [7% (19)], indicating that certain population studies may be underpowered to detect genetic effects specific to dependence (20). The frequency of AUD in the MVP, on the contrary, was much higher [20%, (18)]. Despite these limitations, population based cohorts provide a cost-effective strategy for obtaining very large samples, compared to traditional study designs that require obtaining a diagnosis from clinically trained staff.

Recent discoveries on the molecular genetics of alcohol use behaviors

Table 1 summarizes the most recent GWAS of alcohol use behaviors ($N = 16$); **Figure 2** provides an overview of the chronology of these studies. **Figure 3** shows that the list of genes identified by these studies is highly heterogeneous.

These data suggest incomplete genetic overlap between measures of alcohol use behaviors (**Figure 4**), though ascertainment bias and limited power (see **Figure 5**) are likely to be additional contributing factors.

The 4q23 region, which contains the genes for several alcohol metabolizing enzymes, has been associated with multiple alcohol use behaviors. This association is one of the most consistently replicated findings in the field of psychiatric genetics, although the effects are clearly ancestry-specific (7). There appear to be multiple signals in this region, including *ADH1C* (17, 18, 21–24), *ADH4* (18), *ADH5* (21, 23) and the *METAP1/EIF4E* region (21–23). The GSCAN consortium recently showed that there are at least 13 independent signals with minor allele frequencies over 0.001 at 4q23 (21). Intriguingly, several of those loci are also strongly implicated in non-psychiatric, somatic traits (25).

Beyond the alcohol metabolizing genes, the region containing the genes beta-klotho (*KLB*) and the Fibroblast growth factor 21 (*FGF21*) has been robustly associated with alcohol consumption. The AlcGen consortium was the first to show that the A allele of rs11940694 (**Figure 2**), located in the intron of *KLB*, was associated with reduced alcohol consumption (15). This finding has since been replicated (**Table 1**) - the same SNP was associated with alcohol consumption (17, 18, 22, 23) and alcohol misuse (22). Beta-klotho is a transmembrane protein that acts as a cofactor for the circulating hormone fibroblast growth factor 21 (**FGF21**) by facilitating its binding to FGF receptors (**FGFR**). Interestingly the *FGF21* gene, which is located on chromosome 19, was also associated with AUDIT scores at the gene-level in humans (22). Beta-klotho is primarily expressed in the liver, adipose tissue and pancreas (26), and recent studies have shown that it regulates brain specific functions related to alcohol consumption in mice. For example, mice lacking brain expressed *Klb* showed increased ethanol preference (15). Furthermore, *FGF21* was found to suppress ethanol consumption in wild-type mice but had no effect on mice lacking *Klb* in the brain. Previous studies have shown that *FGF21* and *KLB* are involved in sweet and alcohol preference in mice (27), and a recent study in humans found increased *FGF21* expression in blood after binge drinking (28). These findings suggest that *KLB* and *FGF21* act as part of a brain-liver endocrine axis that regulates alcohol consumption. Future studies could explore the effects of analogues of *FGF21* on alcohol consumption, which are currently being tested in

clinical trials for the treatment of type 2 diabetes and obesity (29). Although *KLB* and *FGF21* seem to be promising avenues for translational research, it is worth noting that while SNPs in *KLB* are associated with alcohol consumption, they have not yet shown any association with AUD (12, 18). This implies that this system might only be relevant for the regulation of normative consumption, although studies of larger AUD populations may yet reveal a role for these loci in AUD. Furthermore, although the locus probably impacts *KLB*, rs11940694 was found to be an expression quantitative trait locus (**eQTL**) for *RFC1* gene expression in the cerebellum and hemisphere (22, 23).

Another well-replicated locus associated with both alcohol consumption and AUD is the region containing the glucokinase receptor (*GCKR*) gene, whose product is a regulatory protein that is produced by hepatocytes and is involved in the cellular trafficking of glucokinase. A non-synonymous SNP in *GCKR*, rs1260326, was robustly associated with alcohol consumption in the MVP, UKB and 23andMe samples (**Table 1**). Intriguingly, rs1260326 has also been previously associated with multiple metabolic traits, including diabetes, obesity and liver disease (30, 31). Given that alcohol consumption is strongly associated with both metabolic and lipid profiles (e.g. 25, 32, 33), it is not clear whether the association with rs1260326 pinpoints a pleiotropic process central to metabolic traits, or whether alcohol causally impacts glucose metabolism and lipid levels, in part via *GCKR*. A recent study characterized the effects of alcohol in neural cell cultures derived from induced pluripotent stem cells (**iPSCs**) and found that genes down-regulated upon alcohol exposure were involved in cholesterol homeostasis in the brain (34). These findings could suggest that AUD has both psychiatric and metabolic components, a theme that has also been suggested for other psychiatric disorders, such as anorexia nervosa (35). Additional evidence supporting this provocative hypothesis is the fact that several genes associated with alcohol use and dependence involve brain-endocrine-metabolic mechanisms. *KLB* is part of a brain-liver feedback loop, acetaldehyde modulates a number of ethanol effects in the brain, and enrichment analyses of alcohol-associated genes found glutamatergic enrichment not only in the brain but also in glucose and carbohydrate processing pathways (21). The ability to process caloric alcoholic beverages may be linked to individual differences in alcohol consumption.

In general, the ‘candidate genes’ for AUD that were examined in smaller cohorts have not been replicated by larger and better powered GWAS (10). One exception is the corticotropin releasing hormone receptor 1 (*CRHR1*), a candidate gene extensively studied in humans and rodents before the advent of large-scale GWAS studies (10). *CRHR1* is central to the cortisol stress response as part of the hypothalamic-pituitary-axis. Extensive preclinical literature has shown that *CRHR1* is associated with relapse to drug taking in mice [e.g. (36, 37)] and there is some evidence that variation in *CRHR1* modulates the role of psychological stress on alcohol intake (e.g. 38, 39). Encouragingly, the genomic region surrounding *CRHR1* has been associated with alcohol consumption and misuse in several recent GWAS studies (21, 22, 40). However, *CRHR1* is located in an inversion polymorphism of roughly 900kb that is common in Europeans and induces extensive LD spanning many genes (41), including *CRHR1* and *MAPT* (22). *MAPT* encodes the protein tau, is involved in Parkinson’s and Alzheimer’s disease. Further work is therefore required to determine which variant(s) are causal, as the inversion in this region complicates the ability of GWAS to fully address this question.

Recent GWAS have identified several regions containing a set of genes that have pleiotropic effects on many psychiatric disorders and related traits; these genes may be tagging a latent factor (“p-factor”) (42). For example, the largest GWAS of alcohol and smoking, which used over 1 million individuals, performed a multivariate GWAS approach to show that 150 loci were associated with multiple substance use phenotypes; variation at *PDE4B* and *CUL3* were associated with both smoking (initiation, cessation, quantity) and drinks per week. Similarly, *CADM2* has been recently associated with alcohol and cannabis use (21, 23, 43). *CADM2* is a cell adhesion molecule (CAM) that influences brain wiring and appears to have a role in multiple neuropsychiatric disorders (44). There is now mounting evidence from independent GWAS showing an association between common genetic variants at *CADM2* and risky or impulsive behaviors including risk tolerance, automobile speeding propensity, number of sexual partners (45), sensation seeking and drug experimentation (46), cannabis initiation (47), and obesity and body mass index (48–50). *CADM2* has also been associated with cognitive phenotypes, including educational attainment (51, 52). We therefore hypothesize that genetic variation at

CADM2 may underlie a latent personality trait or risk factor that predisposes individuals to engage in risky actions (i.e. drinking behaviors).

Despite the success of GWAS of alcohol use (**Figure 4**) the mechanisms by which these newly identified genetic associations exert their effects are largely unknown. More importantly, alcohol consumption and misuse (core traits associated with development of AUD) appear to have distinct genetic architectures (**Table 1, Figure 3**). Ever-larger studies, particularly those extending mere alcohol consumption phenotypes, are required to find the genetic variants that contribute towards the transition from normative alcohol use to misuse, and development of AUD.

Polygenic methods generate hypotheses to test across alcohol use behaviors

One successful application of GWAS has been their use for assigning polygenic risk scores (**PRS**), which provide estimates of an individual's genetic risk of developing a given disorder. Reassuringly, PRS for alcohol use behaviors predict equivalent phenotypes in independent cohorts [e.g. alcohol consumption (53), AD (12), AUD symptoms (54)]. Johnson et al (2019) recently identified that, compared to PRS for alcohol consumption (AUDIT-C), PRS for alcohol misuse (AUDIT-P) were superior predictors of a range of alcohol-related phenotypes, particularly those pertaining to the domains of misuse and dependence. These findings further illustrate that alcohol consumption alone may not be a good proxy for AUD.

PRS can also be used to test specific hypotheses; for example, PRS can be used to measure how environmental, demographic, and genetic factors interact with one another. Are there developmental windows where the effects of alcohol use and misuse are more invasive? Can we identify biomarkers that would inform the transition from normative alcohol use to excessive use and dependence? For instance, the alcohol metabolizing genetic effects on alcohol use appeared to be more influential in later years of college than in earlier years (55, 56), revealing that the nature and magnitude of genetic effects vary across development.

It is worth noting important limitations of PRS analyses. First, polygenic prediction is influenced by the ancestry of the population studied. For example, PRS

for AUD generated in an African American (**AA**) cohort explained more of the variance in AUD than PRS derived from a much larger cohort of European Americans (12). This illustrates that the prediction from one population to another does not perform well (e.g. PRS based on European Americans but used to predict in AA) (57). Second, the method of ascertainment may bias the results. As an example, PRS for DSM-IV AD derived from a population based sample predicted increased risk for AD in other population samples but did not associate with AUD symptoms in a clinically ascertained sample (54). Third, the variance explained by PRS is still low, and hence PRS have limited clinical application. For example, in the largest study of alcohol consumption (21), the alcohol consumption PRS accounted for only ~2.5% of the variance in alcohol use in two independent datasets. Recent work suggested that predictions may improve by incorporating functional genomic information. For example, McCartney et al (58) showed that, compared to conventional PRS, risk scores that took into account DNA methylation were better predictors of alcohol consumption (12.5% vs PRS 0.7%; but see (59)). Nonetheless, the way in which such methods can be used for prevention or treatments of AUD has yet to be established. Lastly, it remains to be determined the nature of these associations. Mendelian randomization analyses can serve to further understand and explore the correlations between alcohol use behaviors and comorbid traits (see **Supplemental 1**).

Alcohol consumption and misuse show a distinct genetic architecture

Before the era of large-scale genomic research, twin and family-based studies identified a high degree of genetic overlap between the genetic risk for AUD and psychopathology by modeling correlations among family members (e.g. (60)). With the recent development of linkage disequilibrium score regression (**LDSC**), it is now possible to estimate the genetic correlations between specific alcohol use behaviors (**Figure 1, Figure 4**) and a plethora of psychiatric, health and educational outcomes using GWAS summary statistics. Most notably, the genetic overlap between alcohol consumption and AD was positive but relatively modest ($r_g = 0.38$ - 0.52 , 12, 18), suggesting that, although the use of alcohol is necessary to develop AD, some of the genetic liability is specific to either levels of consumption or AD.

Another consistent finding from genetic correlation analyses has been that alcohol consumption and AUD show distinct patterns of genetic overlap with disease traits (**Figure 4**). Counterintuitively, alcohol consumption tends to correlate with desirable attributes including educational attainment and is negatively genetically correlated with coronary heart disease, type 2 diabetes and BMI (18, 21–23). These genetic correlations are unlike those observed when analyzing alcohol dependent individuals: AD was negatively genetically correlated with educational attainment (18) and positively genetically correlated with other psychiatric diseases, including major depressive disorder (**MDD**), bipolar disorder, schizophrenia and attention-deficit/hyperactivity disorder (ADHD, 12, 18). Importantly, alcohol consumption (AUDIT-C) and misuse (AUDIT-P or AUD) measured in the same population (UKB or MVP) showed distinct patterns of genetic association with psychopathology and health outcomes (18, 22). This set of findings emphasize the importance of deep phenotyping and demonstrates that alcohol consumption and problematic drinking have distinct genetic influences.

Ascertainment bias may explain some of the paradoxical genetic correlations associated with alcohol consumption (61). Population based cohorts, such as UKB and 23andMe, are based on voluntary participation and tend to attract individuals with higher education levels and socioeconomic status than the general population and, crucially, lower levels of problem drinking. In contrast, ascertainment in the PGC and MVP cohorts (12, 18) was based on DSM-IV AD diagnosis and ICD (International Classification of Diseases) codes for AUD, respectively. Collider bias (the biased estimation of the causal effect of an exposure on an outcome) has been proposed to underlie some of the genetic correlations between alcohol consumption and BMI (62); however, BMI has been consistently negatively correlated with alcohol use in several subsequent studies (18, 21, 22, 63). Furthermore, it is also possible that the genetic overlap between AD and aspects of alcohol consumption are dependent on the specific patterns of drinking. For example, Polimanti et al (64) identified a positive genetic correlation between AD and alcohol drinking quantity ($r_g = 0.75$), but not frequency.

Limitations and future directions

Prior to the availability of large population studies and collaborative consortia efforts, few genes were reliably associated with AUD. The use of intermediate traits or endophenotypes (such as alcohol consumption as an intermediate phenotype for AUD) has become increasingly common and hundreds of new loci have now been associated with alcohol use behaviors. Using intermediate phenotypes also facilitates translational research; we can mimic aspects of human alcohol use using animal models, including alcohol consumption, novelty response, impulsivity, withdrawal and sensitivity (e.g. 65, 66). Animal models provide an opportunity to evaluate the role of newly identified genes (**Table 1**) at the molecular, cellular and circuit level. We may also be able to perform human genetic studies of specific components of AUD such as DSM-IV AD criterion count (67) and alcohol withdrawal (68). To date these traits have only been studied in smaller samples but this approach will be invaluable as sample sizes increase.

Another challenge for AUD genetics is that AUD is a dynamic phenotype, even more so than other psychiatric conditions, and therefore may necessitate yet larger sample sizes. Ever-larger studies, particularly those extending mere alcohol consumption phenotypes, are required to find the genetic variants that contribute towards the transition from normative alcohol use to misuse, and development of AUD. Furthermore, genetic risk unfolds across development, particularly during adolescence, when drug experimentation is more prominent and when the brain is most vulnerable to the deleterious effects of alcohol (69). The Adolescent Brain Cognitive Development (**ABCD**), with neuroimaging, genotyping and extensive longitudinal phenotypic information including alcohol use behaviors (70), offers new avenues for research, namely to understand how genetic risk interacts with the environment across critical developmental windows. Population biobanks aligning genotype data from thousands of individuals to electronic health records are also promising emerging platforms to accelerate AUD genetic research (71).

Despite these caveats, the GWAS described in **Table 1** have already vastly expanded our understanding of the genetic architecture of alcohol use behaviors. It is evident that alcohol use behaviors, like all complex traits, are highly polygenic (11). The proportion of variance explained by genetic variants on GWAS chips (SNP-heritability) ranges from 4 to 13% (**Figure 4**). It is possible that a significant portion

of the heritability can be explained by SNPs not tagged by GWAS chips, including rare variants (46). For instance, a recent study showed that rare variants explained 1-2% of phenotypic variance and 11-18% of total SNP heritability of substance use phenotypes (72). Nonetheless, rare variants are often not analyzed when calculating SNP heritability, which can lead to an underestimate of polygenic effects, as well as missing biologically relevant contributions for post-GWAS analyses (73). Equally important is the need to include other sources of -omics data when interpreting genetic findings, and the need to increase population diversity (see **Supplemental 2**). Therefore, a multifaceted approach targeting both rare and common variation, including functional data, and assembling much larger datasets for meta-analyses (particularly for alcohol misuse and clinical phenotypes) in ethnically diverse populations, is critical for identifying the key genes and pathways important in AUD.

Conclusion

AUD is a complex, heterogeneous disorder encompassing a variety of behavioral, psychological, and physiological traits with a complex longitudinal structure, thus posing an enormous challenge for genetic analysis. Instead, AUD can be fractionated into dimensions or symptoms. Several recent GWAS have used this approach, and it is now common to study quantitative measures, including alcohol consumption and aspects of disordered drinking, in large population samples. As a result, GWAS of alcohol use, misuse and AUD are now beginning to uncover genetic signals that have the potential to be further analyzed at the molecular, cellular, and circuit level in cellular and animal model systems. Findings from polygenic prediction and genetic correlation analyses, which are major trends in psychiatric genetics, have demonstrated that alcohol use behaviors share a common genetic basis with numerous psychiatric, educational and health outcomes. Unsurprisingly, even though studying alcohol consumption has shown some utility, it is apparent that this phenotype cannot be used as a proxy for AUD. We anticipate that big datasets, including those from electronic health records, will revolutionize the field in the years to come.

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FIGURE LEGENDS

Figure 1. The downward spiral of alcohol use disorders. There is an initial prodromal stage during which certain individuals may be at increased risk to be exposed to alcohol. Personality traits such as sensation seeking are thought to promote alcohol experimentation, and transition to a more regular use of alcohol. As alcohol use patterns become more frequent, and tolerance develops, individuals are more likely to loss control over alcohol drinking behavior; risk factors, such as impulsivity, are considered to promote the transition to a more harmful use of alcohol. Alcohol intake may then become inflexible and compulsive, leading to hazardous or continuous alcohol use despite the negative physical and psychological consequences, and ultimately stagnating into dependence. Attempts to quit or cut-down may become apparent; these may be followed by an aversive negative affective state, or withdrawal, thereby increasing the urges to use alcohol, precipitating relapse, and thus perpetuating the spiral of alcohol use disorders.

Figure 2. Timeline of major findings in alcohol use behaviors (alcohol use, yellow; alcohol sensitivity and withdrawal, light orange; alcohol misuse, orange; alcohol dependence and AUD, dark orange) using GWAS methods. Not all references in Table 1 are included in this figure.

Figure 3. Gene-Phenotype network. Shared and specific genetic contributions at different stages or symptoms associated with alcohol use disorders, including alcohol use, indices of alcohol misuse severity (MaxDrinks, AUDIT-P), alcohol dependence, response to alcohol. Only SNPs in genes showing a significant ($P < 10^{-8}$) association with multiple AUD and alcohol-related traits, and available from the GWAS catalog at the time of this writing, are included. *AUDIT*, Alcohol Use Disorder Identification Test; *AUDIT-C*, Alcohol Use Disorder Identification Test items 1-3; *AD*, alcohol dependence; *AUD*, *alcohol use disorder*; *UKB*, UK Biobank; *MVP*, Million Veterans Program; *AlcGen*, Alcohol Genome-wide Association Consortium; *GSCAN*, GWAS & Sequencing Consortium of Alcohol and Nicotine use Consortium; *GxE*, gene by environment interaction; *GWAS*, genome-wide association study.

Figure 4. Heritability and genetic correlation estimates across alcohol use behaviors. Values (%) on the diagonal represent SNP-heritability estimates. Blank

boxes represent pairs of traits that are not significantly genetically correlated; - represents a pair of traits that have not been tested.

Figure 5. GWAS hits discovered as a function of sample size and alcohol use behaviors. *AUDIT*, Alcohol Use Disorder Identification Test; *AUDIT-C*, Alcohol Use Disorder Identification Test items 1-3. Interactive plot: <http://rpubs.com/sanchezroige/475742>

TABLE LEGENDS

Table 1. List of genes associated across two or more GWAS of alcohol consumption and/or abuse. Studies are included if they demonstrate an association with the SNP denoted in the table, or with a SNP in LD ($r^2 > 0.6$).

TABLES

Table 1

Chromosome	Nearest gene	SNP	Alcohol consumption	Alcohol abuse / AUD	References
2	<i>GCKR</i>	rs1260326	Y	Y	(17, 18, 21-23)
4	<i>KLB</i>	rs11940694	Y		(15, 17, 21-23)
4	<i>KLB</i>	rs35538052	Y		(18, 21)
4	<i>ADH1B</i>	rs1229984	Y	Y	(12, 17, 18, 21-23)
4	<i>SLC39A8</i>	rs13107325	Y	Y	(17, 18, 21, 22)
2	<i>LINC01833</i>	rs1004787	Y	Y	(17, 18, 21)
17	<i>MAPT/CHRH1</i>	rs62062288	Y	Y	(17, 21, 22)
19	<i>IZUMO/ FGF21</i>	rs281379	Y	Y	(17, 21, 22)
16	<i>FTO</i>	rs35538052	Y		(17, 18)
4	<i>ADH1C</i>	rs14278306 2	Y	Y	(17, 18)
3	<i>CADM2</i>	rs62250685	Y		(21, 23)

List of genes most commonly associated across GWAS of alcohol consumption and/or abuse. Studies are included if they demonstrate an association with the SNP denoted in the table, or with a SNP in LD ($r^2 > 0.6$). Of note, the proximity of the listed SNPs to the nearest gene does not prove that the gene is causal.